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10/517,626	07/28/2005	Gian Luca Araldi	SNI-003US	3939

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EXAMINER

NOLAN, JASON MICHAEL

ART UNIT	PAPER NUMBER
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1626

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PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No. 10/517,626	Applicant(s) ARALDI ET AL.	
	Examiner Jason M. Nolan, Ph.D.	Art Unit 1626	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 16 November 2007.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-7,9,11,12,14-16,18-46 and 49-94 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☒ Claim(s) 1-7,9,11,12,14-16,49,50,90 and 91 is/are allowed.
- 6) ☒ Claim(s) 18-46,51-54,61-89 and 92-94 is/are rejected.
- 7) ☒ Claim(s) 55-60 is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

This Office Action is responsive to Applicants' Amendment After Final, filed 11/16/2007. **Claims 1-7, 9, 11, 12, 14-16, 18-46, & 49-94** are pending in the instant application; of which, **Claims 1, 5, 7, 9, 11, 12, 14-16, 55-60, 92, & 93** are currently amended and **Claim 94** is new. **Claims 8, 10, 13, 17, 47, & 48** are canceled.

Response to Amendment

Applicant's amendments with respect to **Claims 1, 5, 7, 9, 11, 12, 14-16, 55-60, 92, & 93** have been fully considered and are entered. The 102-prior art rejection of **Claims 1-4, 16, 18-46, 49-55, 59, 92, & 93** and the 103-prior art rejection of **Claims 5-12, 14-16, & 60-91** as being unpatentable over Elworthy *et al.* are withdrawn per amendment; however the 103-prior art rejection is maintained for new **Claim 94**. The Objections to **Claims 13, 16, 55-58, & 60** are withdrawn per amendment. *The finality of the last Office Action is **withdrawn** in view of a new rejection.*

Claim Rejections - 35 USC § 103

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claim 94 is rejected under 35 U.S.C. 103(a) as being unpatentable over Elworthy *et al.* (WO 2003008377 A1, 01/30/2003; see US Patent **6,900,336**; priority to US Provisional Serial No. 2001-305,727, filed on 7/16/2001; see IDS), taken alone.

Determination of the scope and content of the prior art (MPEP § 2141.01)

Taught in the reference is a family of compounds comprising a pyrrolidinone core, wherein the nitrogen is substituted with an alkyl, alkyl-aryl, or alkyl-heteroaryl; and the 5-position of the core contains a hydroxy substituted alkene, (see formula I in **Claim 1** of the '336 Patent). Further, compound RN 493036-24-1 is included in the disclosure; see Example 8 in column 41.

The pharmaceutical compositions of the '336 Patent are useful for the treatment of a disease in a mammal that is treatable by the administration of a selective EP₄ prostaglandin agonist (**Claims 23-25**), such as those mentioned in the specification in columns 1 & 2. Therefore, the scope and content of the prior art correlate significantly with the instant application.

Ascertainment of the difference between the prior art and the claims (MPEP § 2141.02)

Claim 94 lists several species that are considered a homologous series to compound RN 493036-24-1; therefore, the difference between the prior art and some of the species in **Claim 94** is the length of the alkylene chain stemming from the pyrrolidinone core alpha to the nitrogen atom. Said species are on page 22: 1st, 2nd, 9th, and 16th species listed, all of which vary in alkyl length (penta, hexa, hepta, nona) from RN 493036-24-1 which is octa. All species contain a carbon chain with a double bond between the 1st and 2nd carbons and a hydroxyl substituent at the 3rd carbon.

Therefore, the instant claims describe a homologous series of compounds of RN 493036-24-1.

Finding of prima facie obviousness--rational and motivation (MPEP § 2142-2413)

To those skilled in the chemical art, one homolog is not such an advance over an adjacent member of a series because chemists knowing properties of one member of the series would, in general, know what to expect in adjacent members. *In re Henze*, 85 USPQ 261 (1950). Said species of the instant claim, as a whole, would have been obvious to one of ordinary skill in the art because the prior art teaches a homolog (RN 493036-24-1) and a subgenus of compounds (R^1 is alkyl) thereof. One of ordinary skill in the art would have been motivated to prepare homologs of the compounds taught in the prior art by Elworthy *et al.* with an expectation of obtaining compounds with biological activity directed towards prostaglandin.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 18 & 61 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Said claims recite the phrase "a disease or disorder associated with prostaglandin" and the scope of this term is unclear, such that it fails to

define the metes and bounds of its limitation. As pointed out by Coleman *et al.* (*Pharm. Rev.* **1994**; see IDS), it is clear that the biological activities of the prostaglandins are extremely diverse. Not only are there numerous prostaglandin receptors, some of which are found throughout the human body. Due to the diversity of receptors and the dispersion of the receptors in the body, one of ordinary skill in the art may interpret any and/or all diseases or disorders as being associated with prostaglandin.

Claims 18-23, 25-31, 33-40, 43, 46, 61-66, 68-74, 76-83, 86, 89, 92, & 93 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Said claims recite the phrase "*susceptible to*" and the scope of this term is unclear, such that it fails to define the metes and bounds of its limitation. There is no explicit definition of "*susceptible to*" in the specification, so a normal implicit definition is implied. There are different patient populations for the plethora of diseases listed within said claims ranging from fertility conditions to inflammatory diseases to AIDS. It is unclear how one of ordinary skill in the art could determine the patient populations for all diseases and who is "*susceptible to*" them. Further, even healthy people are *susceptible to* developing conditions as life progresses; therefore, the claims are drawn to treating healthy a population. Further, the term is indefinite as it could be interpreted as either treating or preventing, rendering the scope of these claims indefinite.

Claim 51 recites a reference to "*said compound*" in the claim twice without presenting a compound from which to reference from. There is insufficient antecedent basis for this limitation in the claim.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 18, 20, 21-30, 32-36, 38, 39, 41-46, 51, 61, 63-79, 81, 82, 84-89, 92, & 93 are rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the enablement requirement. The claims contains subject matter that was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

As stated in the MPEP 2164.01 (a), "There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue."

In the case *In re Wands*, 8 USPQ2d 1400 (1988), factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. § 112, first paragraph, have need described.

They are:

1. the nature of the invention,
2. the state of the prior art,
3. the predictability or lack thereof in the art,
4. the amount of direction or guidance present,
5. the presence or absence of working examples,
6. the breadth of the claims,
7. the quantity of experimentation needed, and
8. the level of the skill in the art.

In the instant case,

The nature of the invention

The nature of the invention of **Claims 18, 20, 21-30, 32-36, 38, 39, 41-46, 51, 61, 63-79, 81, 82, 84-89, 92, & 93** include methods for the treatment of a plethora of diseases utilizing the compounds and compositions according to **Claims 1 & 5**.

The state of the prior art and the predictability or lack thereof in the art

The state of the prior art is that the pharmacological art involves screening *in vitro* and *in vivo* to determine which compounds exhibit the desired pharmacological activities (i.e. what compounds can treat which specific diseases by what mechanism). There is no absolute predictability even in view of the seemingly high level of skill in the art. The existence of these obstacles establishes that the contemporary knowledge in the art would prevent one of ordinary skill in the art from accepting any therapeutic regimen on its face.

The claimed invention is considered highly unpredictable. It is noted that the pharmaceutical art is unpredictable, requiring each embodiment to be individually assessed for physiological activity. *In re Fisher*, 427 F.2d 833, 166 USPQ 18 (CCPA

1970) indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute. *In the instant case*, the claimed invention is highly unpredictable since one skilled in the art would recognize that a group of compounds may act as prostaglandin agonists, but it does not mean that someone of ordinary skill in the art would be able to use the invention to treat the plethora of diseases as claimed.

Prostaglandins, discovered in the 1930s, comprise a diverse family of biologically active lipids derived from the 20-carbon essential fatty acids. Nine prostanoid receptors have been identified so far in mouse and human. The structures, properties, and functions of most of these receptors have been reviewed in the literature, (see Coleman *et al. Pharm. Rev.* **1994**, in IDS). Synthetic prostaglandins have been developed in the literature, of which some mimic certain prostaglandins activities. Some act as agonists and some antagonists. Some are selective for one receptor while others will invariably interact with numerous receptors. For these reasons, the predictability is low and the state of the art requires *in vivo* data to verify the merits of the invention claimed herein.

Currently, there are synthetic prostaglandins on the market for the treatment of gastric ulcers (misoprostol) and erectile dysfunction (alprostadil). Said compounds have been clinically tested and provide support to the instant application if it is shown that the instant compounds perform by the same mechanism of action.

The breadth of the claims

The breadth of Claims 18, 20, 21-30, 32-36, 38, 39, 41-46, 51, 61, 63-79, 81, 82, 84-89, 92, & 93 encompasses methods for using a genus or subgenus of compounds for the treatment of a variety of diseases ranging from fertility conditions to inflammatory diseases to AIDS. Said diseases stem from receptors found throughout the body.

The level of the skill in the art

The level of skill in the art is high. However, due to the unpredictability in the pharmaceutical art, it is noted that each embodiment of the invention is required to be individually assessed for physiological activity by *in vitro* and *in vivo* screening to determine which prostaglandin agonists exhibit the desired pharmacological activity.

The presence or absence of working examples

The Examiner acknowledges the *in vivo* ovulation assay data presented in Applicants specification, found on pages 107-10, the *in vivo* inhibition of Guinea Pig broncho-constriction data found on pages 111-12, and the *in vivo* inhibition of LPS-induced TNF α release in mice data on pages 112-3. Said data enables the claims for methods of treating asthma, some inflammatory conditions related to prostaglandins but not any and/or all inflammatory diseases, ovulatory disorder, and infertility.

However, the *in vivo* effect on penile corpus cavernosum tissue relaxation on pages 113-5 and the *in vivo* effect on bone loss prevention on pages 115-119 do not provide data for the compounds of the instant application.

The quantity of experimentation needed

The quantity of experimentation needed considered undue. One of skill in the art would need to determine which compounds encompassed in the instant claims are would be efficacious in the treatment of the diseases as claimed, i.e. AIDS, inflammatory diseases, etc., if any. Such experimentation would include *in vivo* animal model studies to show that the compounds treat the disease as desired. It is known in the art that the use of prostaglandin receptor agonists as therapeutic agents has been limited by their short half life and non-specific effects, which result in side effects, (see Ebenezar *et al. Expert Opin. Ther. Patents* **2007**, 17(9), 1131-1145). The prostaglandin receptors are found throughout the body and many therapeutic agents in this family act on more than one receptor in tissues. So, although a binding assay may determine which compounds are more selective for one receptor with respect to another, without *in vivo* data one of skill in the art would be face undue experimentation to use the invention as claimed, with no guarantee of success.

Thus, the specification fails to provide sufficient support for the broad use of the prostaglandin agents. *Genentech Inc. v. Novo Nordisk A/S (CA FC) 42 USPQ2d 1001* states, "a patent is not a hunting license. It is not a reward for search, but compensation for its successful conclusion" and "patent protection is granted in return

for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable”.

Therefore, in view of the Wands factors and *In re Fisher* (CCPA 1970) discussed above, to practice the claimed invention herein, a person of skill in the art would have to engage in undue experimentation to use the instantly claimed invention, with no assurance of success.

Claims 51-54 are rejected under 35 U.S.C. 112, first paragraph, as based on a disclosure which is not enabling. The term “*a prostaglandin EP4 receptor agonist*” is not descriptive of the critical or essential subject matter needed to the practice the invention (i.e. a clearly defined compound). Therefore, the claims are not enabled by the disclosure. See *In re Mayhew*, 527 F.2d 1229, 188 USPQ 356 (CCPA 1976). The scope of the term “a prostaglandin EP4 receptor agonist” is so broad as to include any compounds that may fall outside of the teachings from the instant application. Applicant must teach one of ordinary skill in the art how to make and use the invention as claimed. How is the instant disclosure enabling for a compound that may fall outside of the teachings of the instant application, yet have the property of being “a prostaglandin EP4 receptor agonist”?

Examiner suggests an amendment to **Claim 51** to include the compounds of formula II, as claimed in **Claim 55** in order to overcome this rejection.

Claim Objections

Claims 24, 41, 42, 44, 45, 55-60, 67, 84, 85, 87, & 88 are objected to as being dependent upon a rejected base, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Claims 19-46 & 61-89 are objected to because of the following informalities: the claim language is not indicative of what the invention is. For example, Claim 28: "A method of claim 18 wherein the mammal is suffering from or susceptible to AIDS." Said Claim is not indicative of treating a disease, but instead claims "treating a mammal." For clarity, the claim should read, for example: "A method of claim 18 wherein the disease is AIDS." Appropriate correction is required.

Conclusion

Claims 1-7, 9, 11, 12, 14-16, 49, 50, 90, & 91 are allowed.

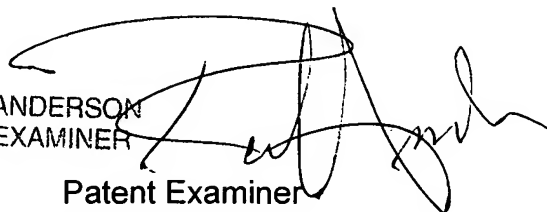
Telephone Inquiry

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Jason M. Nolan, Ph.D.** whose telephone number is **(571) 272-4356** and electronic mail is **Jason.Nolan@uspto.gov**. The examiner can normally be reached on Mon - Fri (9:00 - 5:30PM). If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Joseph M^cKane** can be reached on **(571) 272-0699**. The fax phone number for the organization where this application or proceeding is assigned is **571-273-8300**. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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A handwritten signature in black ink, appearing to read 'Rebecca Anderson', is written over the printed name and title of the Primary Examiner.